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| 10/523,655 | 02/04/2005 | Alan P. Escher | 14102-1US | 3703 |

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| EXAMINER | |
|---|---|
| WEHBE, ANNE MARIE SABRINA | |
| **ART UNIT** | **PAPER NUMBER** |
| 1633 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/523,655 | ESCHER ET AL. | |
| | Examiner | Art Unit | |
| | Anne Marie S. Wehbe | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2 and 5-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 5-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's amendment and response to the restriction/election requirement received on 6/26/07 has been entered. Applicant's election of a polynucleotide construct comprising a nucleotide sequence encoding BAX and an autoantigen is acknowledged. As applicant did not provide any arguments traversing this election, the election is considered to have been made without traverse. Claims 3-4, and 19-24 have been canceled. Claims 1-2, and 5-18 are currently pending and under examination in the instant application. An action the merits follows.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 and 5-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses polynucleotide constructs comprising a polynucleotide sequence encoding Bax and a polynucleotide sequence encoding an autoantigen for preventing, delaying the onset of or treating an autoimmune disease. However, neither the instant

specification nor drawings provides sufficient written description for a the genus of polynucleotide constructs encompassed by the claims, and in particular for the genus of polynucleotide sequences encoding autoantigens associated with autoimmune diseases.

As an initial matter, the methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

The specification fails to adequately describe the genus of polynucleotide sequences encoding autoantigens associated with the numerous known autoimmune diseases, of which the specification indicates that there are approximately 80, which can be utilized in the disclosed polynucleotide constructs to prevent, delay the onset of or treat any autoimmune disease. The teachings of the specification are limited to the disclosure of a single autoantigen, GAD, which stands for glutamic acid decarboxylase, which is a known autoantigen for type 1 diabetes. The specification provides no further disclosure of any other autoantigen for type 1 diabetes or for any other autoimmune disease. It is further noted that while the specification on page 1 indicates that there are approximately 80 autoimmune diseases, the specification provides no disclosure of the number of potential or known autoantigens associated with any of the 80

diseases. Thus, the specification fails to set forth in terms of distinguishing identifying characteristics as evidenced by descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the genus of autoantigens for autoimmune diseases. In addition, concerning GAD, the specification teaches that two sequences, one which encodes the non-secreted cytoplasmic GAD, GAD65 (SEQ ID NO:5), and the other encodes a secreted GAD, sGAD55 (SEQ ID NO:62). The specification teaches that of the two, only sGAD55 was shown to have any therapeutic effect on type 1 diabetes when administered in combination with a polynucleotide encoding Bax. Thus, the specification indicates an additional level of complexity beyond the simple identification of an autoantigen associated with an autoimmune disease, as clearly different forms of the autoantigen can substantially effect the activity of the autoantigen *in vivo*. In addition to the failure of the specification to disclose other species of autoantigens, the specification also fails to describe the particular structure of any other species of autoantigen that is capable of preventing/treating an associated autoimmune disease in the context of the claimed invention.

*Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The instant specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American*

*Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). The applicant has not provided any description or reduction to practice of constructs comprising a polynucleotide encoding an autoantigen other than polynucleotide sequences encoding the GAD autoantigen associated with type 1 diabetes, and further has not provided a description of any polynucleotide sequence other than SEQ ID NO:62, secreted GAD55, which is capable of having any therapeutic effect on type 1 diabetes in the context of a polynucleotide construct encoding both an autoantigen and Bax. Based on the applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the polynucleotide sequences encoding autoantigens encompassed by the claims, nor determine which sequences from the genus would be capable of preventing/treating the associated autoimmune disease when administered in the context of a polynucleotide construct as claimed. Further, the specification does not disclose any shared physical, structural, or functional characteristics of GAD which are shared by the genus of autoantigens as a whole, or provide guidance as to how other autoantigens from any autoimmune

disease including type 1 diabetes can be identified, isolated, and potentially modified for use in the instant invention. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel,* 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. Thus, for the reasons outlined above, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention because it does not provide adequate written description for the genus of polynucleotide sequences encoding autoantigens capable of preventing/treating any autoimmune disease in the context of the claimed polynucleotide construct.

Claims 1-2, and 5-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) a method of inhibiting the development of diabetes type 1 in a patient comprising administering by intramuscular injection a plasmid DNA which comprises a polynucleotide sequence encoding soluble GAD 55 (sGAD 55) and a polynucleotide sequence encoding Bax operatively linked to a CMV promoter, 2) a plasmid DNA for inhibiting the development of diabetes type 1 which comprises a polynucleotide sequence encoding soluble GAD 55 (sGAD 55) and a polynucleotide sequence encoding Bax operatively linked to a CMV promoter, does not reasonably provide enablement for methods for preventing, delaying the onset of or treating any pre-existing autoimmune disease in a patient by administering by any route of administration any polynucleotide construct encoding Bax and one or more autoantigens for the autoimmune disease. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification discloses polynucleotide constructs comprising a polynucleotide sequence encoding Bax and a polynucleotide sequence encoding an autoantigen for preventing, delaying the onset of or treating an autoimmune disease, and methods for preventing, delaying the onset of or treating an autoimmune disease comprising administering a polynucleotide sequence encoding Bax and a polynucleotide sequence encoding an autoantigen. The claims read broadly on preventing/treating any autoimmune disease using any associated autoantigen. The claims further read broadly on using any route of administration of the polynucleotide construct. IT is also noted that the constructs as claimed do not comprise any transcription/translation control elements such that the claims read broadly on construct which are not capable of expressing the encoded polynucleotide sequences.

The specification, while broadly disclosing the treatment of any autoimmune disease is primarily focused on the treatment of type 1 diabetes. The only disclosure of autoimmune diseases other than diabetes occurs on page 1 of the specification which states that there are approximately 80 autoimmune diseases of which systemic lupus, rheumatoid arthritis, and multiple sclerosis, and type 1 diabetes are examples. The remainder of the specification, however, is solely focused on diabetes and provide no further guidance for treating systemic lupus, rheumatoid arthritis, multiple sclerosis or any of the other 80 or so known autoimmune diseases. It is further noted that the specification fails to provide any guidance as to an autoantigen suitable for use in the therapeutic polynucleotide constructs comprising a polynucleotide sequence encoding Bax and a polynucleotide sequence encoding an autoantigen

other than the soluble secreted form of GAD, sGAD55 (SEQ ID NO:62). The specification is silent as to the identity of any other autoantigen besides GAD and further lacks guidance for identifying, isolating, and/or modifying any other autoantigen such the expression of the autoantigen in combination with Bax would be capable of having any therapeutic effect on the development, severity, or persistence of any autoimmune disease associated with the autoantigen. It is further noted that the specification does not disclose any polynucleotide construct other than a plasmid DNA which comprises 5' to 3' a CMV promoter, a polynucleotide encoding an autoantigen, an IRES, and polynucleotide sequence encoding Bax. The specification fails to provide any disclosure regarding alternative expression constructs or promoters, or provide any guidance as to the use of constructs lacking expression elements. The applicant is reminded that the Federal Circuit has stated:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.
> Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997).

Turning to the working examples, the specification teaches the construction of two polynucleotide constructs, both plasmid DNAs, one of which comprises 5' to 3' a CMV promoter, a polynucleotide encoding cytoplasmic GAD65 (SEQ ID NO:5), an IRES, and polynucleotide sequence encoding Bax, and the other which comprises a CMV promoter, a

polynucleotide encoding secreted GAD55 (SEQ ID NO:62), an IRES, and polynucleotide sequence encoding Bax. The specification further teaches that of the two, only the construct encoding sGAD55 and Bax was shown to have any therapeutic effect on type 1 diabetes when administered by intramuscular injection to 4-5 week old female NOD mice, a mouse model of type 1 diabetes. The working example states that of the mice which received the plasmid encoding sGAD55 and Bax, only 47% developed diabetes compared with 93% incidence in unvaccinated control mice. However, the specification also teaches that the administration of plasmid encoding sGAD55 and Bax did not have any effect on the onset or severity of disease, as the mice in this group which developed diabetes, showed symptoms at the same time as the control group, see specification pages 8-9. The working example also teaches that this plasmid did not significantly suppress Th-1 like activity but did appear to reduce Th-1 like activity as measured by the ratio of IgG isotypes. Thus, from the working examples, it is clear that plasmid DNA encoding sGAD55 and Bax cannot delay the onset of diabetes as claimed, but can suppress the development of type 1 diabetes. As can be seen from the analysis above, the ability of the plasmid to treat pre-existing diabetes was not evaluated.

While the working example discussed above provides evidence for enablement of the specific intramuscular administration of plasmid DNA encoding Bax and sGAD55 to suppress type 1 diabetes, the success of the working examples cannot be extrapolated without undue experimentation to the use of other autoantigens in diabetes, or in the prevention/treatment of other autoimmune disease. At the time of filing, the state of the art of preventing or treating autoimmune disease by genetic vaccination with autoantigens was considered undeveloped and unpredictable. For example, Mathisen and Touhy teach that conflicting results have been

obtained in attempts to use DNA vaccination to prevent or suppress EAE in mice, a model system for multiple sclerosis. They report that while some groups have had success in induced resistance to EAE development by administering DNA encoding an immunodominant PLP epitope or an immunodominant MBP epitope fused to an IgG Fc receptor, others have shown the prevaccination with constructs encoding PLP protein or its encephalitogenic peptides enhances EAE induction (Mathisen and Touhy (2000) J. Clin. Immunol., Vol. 20(5), 327-333, page 327, column 1). Mathisen and Touhy also state that, "..the erratic and seemingly unpredictable clinical outcomes that result from DNA vaccination clearly indicate that more work is necessary in order to elucidate the mechanism of DNA vaccination in EAE and explain the paradoxical experimental results derived from different rodent strains and DNA constructs" (Mathisen and Touhy, supra, pages 327-328, bridging paragraph). It is further noted that the experiments described in Mathisen and Touhy demonstrate that different autoantigens associated with the same autoimmune disease exhibit different abilities to affect autoimmune responses. Trucco et al. teaches that while a number of autoimmune disease including MS and type 1 diabetes are self protein driven, others like Crohn's disease and lupus exhibit immune destruction and immune reactivities against diverse cell types and self-proteins, with no evidence of a specific antigen or set of related antigens (Trucco et al. (2002) Curr. Gene Ther., Vol. 2, 341-354, page 341, column 1). Based on these issues, Trucco et al. states that for these and other similar autoimmune diseases with complex and as yet undefined etiologies, antigen-directed therapy will be more challenging (Trucco et al., supra, page 341, column 1). Trucco et al. also teaches that at the time of filing there were no cures for autoimmune diseases, including diabetes and rheumatoid arthritis, and that once tissue destruction has occurred at the moment of clinical onset, there is

very little that can be done other than transplantation of replacement cells (Trucco et al., page 341, column 2). Thus, Trucco et al. establishes that different autoimmune disease have substantially different etiologies which materially affect their ability to be treated using the strategy of autoantigen immunization. Simone et al. further highlights the potential risks of DNA vaccination for treatment of autoimmune diseases, including the danger of stimulating the immune system against the autoantigen instead of the reverse thus worsening or even initiating autoimmune disease, and provides examples where immunologic vaccination has in fact exacerbated autoimmunity (Simone et al. (1999), Diabetes Care, Vol. 22 (2), B7-B15, page B11). Thus, at the time of filing, the skilled artisan would not have predicted success in preventing, delaying or treating any autoimmune disease *a priori*, with a plasmid DNA encoding an autoantigen. It is further noted, regarding the administration of a polynucleotide encoding Bax, that the prior art is silent as to the predictability or unpredictability of using Bax to prevent or treat autoimmune diseases. At the time of filing, constructs encoding Bax had only been used in a therapeutic setting to induce apoptosis in tumors. Thus, the nature of different autoimmune diseases and the state of the art of autoantigen based genetic therapies of autoimmune diseases does not support a correlation between the success using a plasmid DNA encoding a single modified sGAD55 autoantigen and Bax in suppressing diabetes with the prevention, delay of onset or treatment of any autoimmune disease by administering any construct encoding an autoantigen and Bax.

In summary, in view of the state of the art at the time of filing concerning the differences in autoimmune diseases and the unpredictability in DNA based immunization strategies for treating autoimmunity as discussed in detail above, the lack of guidance provided in the

specification, including the working examples, concerning autoantigens associated with autoimmune diseases other than GAD and diabetes, and for vectors other than plasmid DNA and administration routes other than intramuscular injection, the requirement for modification of the GAD protein for therapeutic activity in the instant methods, and the breadth of the claims, it would have required undue experimentation at the time of filing for the skilled artisan to make and use the scope of the invention as claimed.

The claims are free of the prior art of record, as the prior art of record does not teach or suggest combining the expression of Bax with the expression of an autoantigen to treat an autoimmune disease by administering a polynucleotide construct encoding both Bax and the autoantigen.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D.; whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

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